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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,482	09/25/2000	P. Martin Petkovich	57600/00035	3039

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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,482	PETKOVICH ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83-95,97-102 and 104-112* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-95,97-102,104-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed May 31, 2002 amending the specification to insert sequence identifiers and correct typographical errors, amending claims 83-85, 89-92, 95, 97, 99, 101 and 104-106, adding claims 107-112 and canceling claims 96 and 103 has been entered.

Claims 83-95, 97-102 and 104-112 are pending.

Information Disclosure Statement

In their Remarks field May 31, 2002, page 17, Applicants in refer to concurrently filed IDS as "supplemental IDS". The examiner notes that IDS filed May 31, 2002 is the only IDS in the file.

Specification

The disclosure is objected to because of the paper and computer readable forms of the Sequence Listing are not identical. A substitute paper copy of the Sequence Listing identical to the computer readable form in the file is required. It should be accompanied by the statement the two forms are identical and by the amendment directing the entry of a substitute Sequence Listing.

Claim Objections

Claims 83 and 90 are objected because of the following. The Markush group requires "and" before the last member of the group (line 8).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass all polypeptides of any function that bind to any antibody specific to for SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:32. The Examiner is unable to locate adequate support in the specification for such polypeptides. Thus there is no indication that polypeptides encompassed by claims 96-106 were within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite "a conservatively substituted amino acid variant" of the amino acid sequences encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a DNA that hybridizes thereto or to a degenerate variant thereof under specific conditions. This amounts to any structure having the same function as a protein encoded by SEQ ID NOs: 3, 5 or 31. The structural limitations are insufficient because while a substitution is required to be conservative any amino acid residue in the sequence can be substituted resulting in a completely novel structure that is not described. This is equivalent to a claim with no structural limitations wherein an enzyme is defined by the function only. Furthermore, the function described only as "oxidizes/hydroxylates a retinoid" encompasses many different functions. In addition, a genus of degenerate variants of SEQ ID NOs: 3, 5 or 31 is enormous.

Claims 83, 86-90, 93-95 and 107-112 are included in this rejection because the function recited in the claims encompasses any oxidizing/hydroxylating activity with substrate specificity as broad as any retinoid, i.e., retinoic acid (RA), retinal, retinol in every stereo configuration as well as undescribed natural and artificial variants thereof (see the specification, paragraph bridging pages 5 and 6). At most, the claims limit the enzymatic activity to hydroxylating any retinoid at the 4-position of the β-ionone ring without specifying the retinoid.

The specification discloses only a single species of the claimed genus, a retinoic acid inducible protein having all-*trans* retinoic acid 4-hydroxylase activity, which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Claims 97-102 and 104-106 are drawn to a polypeptide that binds to an antibody specific for SEQ ID NOs: 2, 4 or 32 and has no known function.

Therefore, the claims are drawn to a genus of polypeptides of any function. The genus of polypeptides that comprises these above polypeptide molecules is a large variable genus encompassing many different proteins and fragments thereof. Many functionally unrelated polypeptides are encompassed within the scope of these claims, including partial sequences. It encompasses both a polypeptide having an enzymatic activity and an inactive variant thereof. The art does not allow the predictability of function based on the structure.

Thus, a conservatively substituted amino acid variant of a polypeptide having ability to oxidize a retinoid, hydroxylate a retinoid at the 4-position of the β-ionone ring or a polypeptide that binds to the specific antibody and has no specific function, lack sufficient written description needed to practice the invention of claims 83-95, 97-102 and 104-112.

Claims 84, 85, 91 and 92 are included in this rejection because in view of the amendments to the base claims, claims 84, 85, 91 and 92 now encompass a protein or a variant of said protein.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a all-*trans* retinoic acid 4-hydroxylase encoded by SEQ ID NOs: 3, 5 or 31 or encoded by a sequence that hybridizes thereto under stringent conditions, does not reasonably provide enablement for a conservatively substituted amino acid variant thereof, a retinoid oxidase of any substrate specificity that is encoded by a sequence that hybridizes to SEQ ID NOs: 3, 5 or 31 or a degenerate variant thereof and a conservatively substituted amino acid variant thereof as well as a polypeptide of unknown function that binds to an antibody specific for SEQ ID NOs: 3, 5 or 31. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible derivatives having the desired enzymatic activities.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir.

1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claim, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is

unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any sequence that is claimed in claims 83-95, 97-102 and 104-112 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the requisite activity. The specification does not teach the structure that is responsible for a specific all-*trans* retinoic acid 4-hydroxylase activity as compared to any other retinoid oxidizing activity;(B) the general tolerance of a protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Furthermore, degenerate variants of SEQ ID NOs: 3, 5 or 31 encompass an enormous number of molecules. The specification does not provide any guidance as to which of these degenerate variants can be used, so that a DNA that hybridizes thereto would encode a protein with the requisite [properties.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated

with the scope of the claims broadly including a number of amino acid modifications of SEQ ID NOs: 2, 4 or 32. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a protein having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

Claims 97-102 and 104-106 are drawn to proteins with no function. Applicants have not provided sufficient guidance as to what is the function of proteins encompassed by the claims.

The state of the art does not allow the predictability of the properties based on the structure. Therefore, one skilled in the art would require guidance as to how to use a polypeptide of unknown function that binds to an antibody specific for SEQ ID NOs: 2, 4 or 32 in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83-95, 97-102 and 104-112 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83-95 recite "conservatively substituted amino acid variant thereof". There are no clear assigned definitions of the term "conservatively substituted amino acid variant" in the art.

Claims 84 is unclear because it is unclear how the scope of the claim is affected by the recitation of a degenerate sequence, since said degenerate sequence encodes the same protein as the base sequence.

Claim 89 is confusing because it is unclear whether a variant of an encoded protein is claimed or a variant is encoded by a recited DNA.

Claims 97-102 and 104-112 are confusing because they recite an antibody that is elicited by SEQ ID NO:2, 4 or 32 and by an epitope of unknown structure.

The metes and bounds of claims 107-112 are uncertainable because the difference between "oxidizes" and "hydroxylates" is unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 97, 99, 101 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Vetter et al.

Vetter et al. teach the amino acid sequence of an inducible cytochrome P-450 protein from Periwinkle (*Catharanthus roseus* L.) (page 1002, Figure 3.). Since an epitope is not limited to a specific fragment, this polypeptide will bind to an antibody elicited by an epitope of some five, for example, amino acids within the conserved region of SEQ ID NOs: 2, 4 or 32 and, therefore anticipates claims 97, 99, 101 and 104-112.

Claims 97, 99, 101 and 104-112 are rejected under 35 U.S.C. 102(b) as being anticipated by Shen et al.

Shen et al. teach the amino acid sequence of a mouse cytochrome P-450 protein (page 11485, Figure 3.). Since an epitope is not limited to a specific fragment, this polypeptide will bind to an antibody elicited by an epitope of some five, for example, amino acids within the conserved region of SEQ ID NOs: 2, 4 or 32 and, therefore anticipates claims 97, 99, 101 and 104-112.

Response to Arguments

Applicant's arguments filed May 31, 2002 have been fully considered but they are not persuasive.

Applicants argue that claims 97-102 and 104-112 do not introduce the new matter because the specification on page 36 teaches that "antibodies can be used to detect the proteins of the invention, portions thereof or closely related isoforms in

various biological materials" (page 10). This is not persuasive because there is support for an antibody and a method of use thereof but not for proteins that can be detected using said antibodies.

With regard to conservative variants, applicants disagree that they amount to any protein having the desired function (pages 11-12). Applicants assert that "it is only conservatively substituted variants of these proteins that are claimed. The claim includes only those variant proteins in which an individual amino acid is substituted for another amino acid of protein to have function. ... while it is admitted there is no limitation on the number of such substitutions that might be made, any such substitution is clearly based on one of basic claimed structures(a protein encoded by the sequence that hybridizes to SEQ ID NO:3, 5, etc.) and would be known to the skilled person" (page 12, 2nd paragraph). This is not persuasive because claims are not drawn to proteins having substitutions from other proteins. Ad in any event, there is no limitation on the number and location of residues to be substituted.

Applicants further argue with regard to the function that "applicants reasonable expect that P450RAI oxidizes the 18 position of the β-ionone ring as well as the 4 position, and that P450RAI oxidizes retinol as well as RA (see page 3, lines 23-26)" (page 13, 2nd paragraph). The specification on page 3, lines 23-26 reads differently. However, on page 3, lines 27-30, it provides support for the 4 position of β-ionone ring

of RA. However, the claims recite much broader specificity expanding the scope of the claims to encompass retinoid oxidizing enzymes of different function and properties. With regard to the 102 rejection, applicants argue that "the antibody is elicited by an epitope located within a specified unconserved region of the protein" (page 17). This is not persuasive because within this region the proteins of the instant invention share a few identical or conservatively substituted amino acids with the proteins of the references. An antibody elicited by such fragment would cross react with many proteins including the proteins of the instant invention and the references.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

August 9, 2002